Ultrasound and Clinical Predictors of Recurrent Ischemia in Symptomatic Internal Carotid Artery Occlusion

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Abstract: BACKGROUND AND PURPOSE Occlusion of the internal carotid artery puts patients at risk of recurrent ischemic events because of hemodynamic compromise. Our goal was to characterize clinical and duplex parameters indicating patients at risk of recurrent ischemia. METHODS We retrospectively identified patients with symptomatic internal carotid artery occlusion. Clinical characteristics and ultrasound parameters, including collateral networks, were analyzed. Predictors for recurrent ipsilateral ischemia were investigated by Cox regression analysis. RESULTS Of 68 patients, at least 1 recurrent ischemic event within the same vascular territory was observed in 14 patients (20.6%) within 2 to 92 days (median, 29.5 days). The median follow-up period was 6 months. Diabetes mellitus and previous transient ischemic attack were associated with recurrence, as was activation of the maximum number of collateral pathways on transcranial ultrasound (28.6% versus 5.6%; P=0.03). Furthermore, flow in the posterior cerebral arteries was higher in patients with recurrence in ipsilateral and contralateral posterior cerebral artery P2 segments (76 IQR 37.5 versus 59, IQR 22.5 cm/s and 68, IQR 35.6 versus 52, IQR 21 cm/s; P<0.01 and 0.02). CONCLUSIONS Flow increases in both posterior cerebral artery P2 segments suggest intensified compensatory efforts when other collaterals are insufficient. Together with the presence of diabetes mellitus and a history of transient ischemic attack, this duplex parameter indicates that patients with internal carotid artery are at particular risk of recurrent ischemia.

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Ultrasound and clinical predictors of recurrent ischemia in symptomatic internal carotid artery occlusion

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Abstract

Background and Purpose: Occlusion of the internal carotid artery (ICAO) puts patients at risk of recurrent ischemic events due to hemodynamic compromise. Our goal was to characterize clinical and duplex parameters indicating patients at risk.

Methods: We retrospectively identified patients with symptomatic ICAO. Clinical characteristics and ultrasound parameters including collateral networks were analyzed. Predictors for recurrent ipsilateral ischemia were investigated by Cox regression analysis.

Results: Of 68 patients, at least one recurrent ischemic event within the same vascular territory was observed in 14 (20.6 %) within 2 - 92 days (median 29.5 days). The median follow-up period was 6 months. Diabetes and previous TIA were associated with recurrence, as was activation of the maximum number of collateral pathways on transcranial ultrasound (28.6 vs. 5.6 %, $p = 0.03$). Furthermore, flow in the posterior cerebral arteries (PCA) was higher in patients with recurrence in ipsi- and contralateral PCA- P2 segments (76 IQR 37.5 vs. 59 IQR 22.5 and 68 IQR 35.6 vs. 52 ± 21 cm/s; $p < 0.01$ and 0.02).

Conclusions: Flow increases in both PCA-P2 suggest intensified compensatory efforts when other collaterals are insufficient. Together with the presence of diabetes and a history of TIA, this duplex parameter indicates ICAO patients at particular risk of recurrent ischemia.

Introduction

Patients with symptomatic ICAO are at an increased risk of recurrent stroke, which has been estimated between 5.5-10% per year[1-5]. The risk is likely increased if collateral supply is insufficient resulting in hemodynamic compromise[6-8]. Collateral pathways activated in response to ICAO have been categorized as either primary or secondary. Primary collateral pathways involve the circle of Willis, either through cross flow from the anterior communicating artery (ACoA) or the posterior communicating artery (PCoA). Reversed flow through the ophthalmic artery (OA) or enhanced flow within leptomeningeal collaterals (LPM) are considered secondary collateral pathways [9]. Secondary collaterals may have a limited capacity, and activation of secondary collaterals has been linked to impaired cerebral vasoreactivity [10, 11]. There are, however, studies suggesting that the type of collateral network does not impact cerebrovascular reserve , but that the activation of more collateral pathways indicates a higher risk of stroke recurrence in ICAO [12,13]. The current study aimed to define clinical and ultrasound predictors for recurrent ipsilateral ischemia or early vascular death in patients with symptomatic ICAO.

Methods

Study design and cohort description

In this retrospective analysis, patients with symptomatic proximal ICAO treated at the University Hospital Zurich Department of Neurology between 2009 and 2014 were included if they had received an extra- and intracranial duplex investigation at our site within 30 days and a clinical follow up of at least 1 month (see supplementary methods). Patient demographics, stroke severity on the National Institute of Health Stroke Scale (NIHSS) and medical history prior to stroke were obtained.

Statistical analyses

Analyses were performed using non- and semiparametric methods. Group comparisons were performed using Fisher's exact test (categorical measurements) and 2-tailed Mann-Whitney U-test (continuous measurements) both yielding conservative p-values by ignoring the censoring. Predictors for recurrent ischemia were investigated using a univariate Cox regression model. Multiple testing corrections were omitted.

Results

68 patients with symptomatic ICAO were included in the study (Table 1). At least one recurrent ischemic event within the same vascular territory was observed in 14 (20.6 %) patients at a median time of 29.5 days (IQR 8 – 89) during the median follow up of 6 months (IQR 4 – 24). In the group with an observed recurrent ischemic event, there were significantly more patients with diabetes and previous TIA as well as statin and antiplatelet use in their medical history. First duplex ultrasound was performed within a median time of 1 day (IQR 0.25 – 3) after the ischemic event (Figure 1). In patients with a recurrent event, activation of all four collateral pathways (ACoA, PCoA, LM, OA) was more frequently detected by TCD, but the type of pathway (type I or II) was not different between groups. Higher flow values within both PCA-P2 segments were observed in patients with recurrence (Supplementary Figure 1, supplementary Tables I and II).

According to univariate Cox regression analysis (Supplementary Table III), diabetes and previous TIA with the use of platelet inhibitors and/or statins as well as the presence of four activated collateral pathways were univariately associated with a recurrent ischemic event. Flow in the posterior cerebral arteries was higher in patients who experienced a recurrent event. All other investigated duplex parameters were not significantly different between patient groups.

Discussion

Our data indicate that after symptomatic ICAO, the risk of a recurrent ipsilateral ischemic event is high, particularly in the early phase. We found that the activation of all four TCD-assessable collateral systems (ACoA, OA, PCoA and LPM) and increased flow in both PCA-P2 segments were more common in patients with a recurrent event. This suggests that recruitment of more collateral systems, particularly the vertebrobasilar vessels, implies impaired collateral capacity. MCA flow velocities were not predictive of ischemia recurrence [14].

Summary

Previous TIA and diabetes are clinical parameters associated with increased risk of recurrence after symptomatic ICAO. Presence of four activated collateral systems in transcranial ultrasound and increased flow in the PCA-P2 segments are further indicators of hemodynamic failure and risk of ischemia recurrence. Prospective validation in larger patient groups is needed. However, TCD has the potential to strengthen clinical prediction algorithms due to its unique capability to assess collateral flow pathways.

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Table 1: Patient clinical characteristics

	All n = 68 (%)	No recurrent event observed n = 54 (%)	Recurrent event observed n = 14 (%)	p-value
Demographic data				
Age (Range)	65 (30-90)	64.7(30 – 88)	65.5 (47-90)	0.96
Male	47 (69)	38 (70.4)	9 (64.3)	0.75
Type of event				
TIA	5 (7.4)	4 (7.4)	1 (7.1)	0.6
Retinal ischemia	5 (7.4)	3 (5.6)	2 (14.3)	0.2
Stroke	58 (85.3)	47 (87)	11 (78.6)	0.2
Medical history, n (%)				
Smoking	29 (43)	20 (37)	9 (64.3)	0.21
Hypertension	49 (72)	37 (68.5)	12 (85.7)	0.32
Diabetes	13 (19)	7 (13.0)	6 (42.9)	0.02*
CAD	12 (17.6)	8 (14.8)	4 (28.6)	0.25
pAOD	12 (17.6)	9 (16.7)	3 (21)	0.68
Dyslipidemia	43 (63)	33 (61)	10 (71)	0.47
Atrial fibrillation	10 (14.7)	10 (18.9)	0	0.10
Pre-Stroke Medication, n (%)				
Platelet inhibitor	26 (38)	16 (29.6)	10 (71.4)	<0.01*
Statin	17 (25)	9 (16.7)	8 (57)	<0.01*
Clinical scores, median (IQR)				
NIHSS on admission	3 (9.5)	3.5 (11.8)	3 (5.2)	0.58
NIHSS at 3 months	0.5 (2.3)	0 (2)	1 (3.3)	0.38
mRS on admission	3 (4)	3 (4)	2.5 (2.5)	0.48
mRS at 3 months	1 (2.3)	1 (2.8)	1.5 (1.5)	0.42
Past vascular events, n (%)				
TIA	9 (13.2)	4 (7.41)	5 (35.7)	0.01*
Stroke	6 (8.8)	4 (7.41)	2 (14)	0.42
Retinal artery occlusion	3 (4.4)	2 (3.7)	1 (7.1)	0.58
TOAST, subtype, n (%)				
Large vessel disease	38 (56)	27 (50)	11 (78.6)	0.13
Cardio embolic	8 (11.8)	8 (14.8)	0	0.11
Small artery disease	0	0	0	-
Other causes	17 (25)	15 (27.8)	2 (14.3)	0.62
Undetermined	5 (7.4)	4 (7.41)	1 (7.1)	0.91

Legend Table 1: Clinical characteristics of all 68 patients (All) and patients groups without or with ipsilateral recurrent ischemic event. P values < 0.05 in Mann-Whitney U-test or Fisher Exact Test are marked with *. CAD: coronary artery disease, pAOD: peripheral artery occlusive disease. Numbers (n) and percentage or median and interquartile range (IQR) are shown.

Figure 1

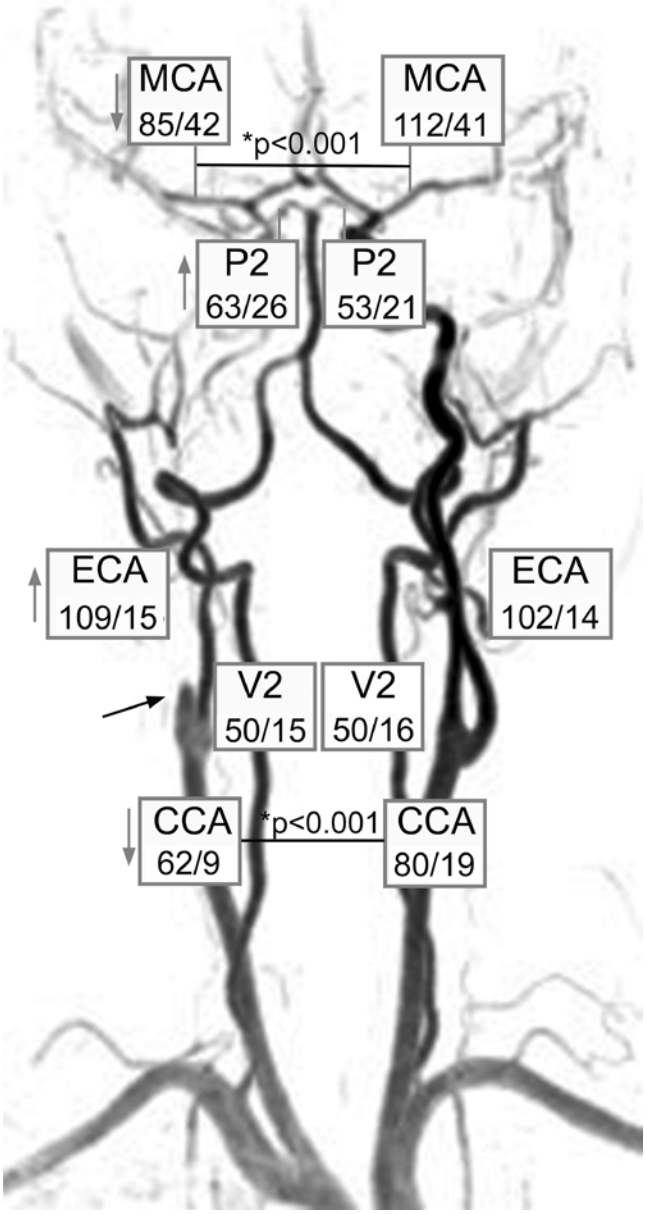

Figure 1: Flow changes in extra- and intracranial arteries induced by ICAO

Median values for PSV/EDV from all patients are superimposed upon characteristic MR angiography image of a patient with ICAO (black arrow). Differences between affected (ICAO) and contralateral side are supported by p-values resulting from Mann-Whitney U-test. Grey arrows illustrate typical flow changes observed ipsilateral to ICAO (direction of change in contrast to contralateral side). The MR angiography image was provided by the Department of Neuroradiology, University Hospital Zurich.